Modifying ligand-induced and constitutive signaling of the human 5-HT4 receptor.

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Public Summary:

Scientific Abstract:
G protein-coupled receptors (GPCRs) signal through a limited number of G-protein pathways and play crucial roles in many biological processes. Studies of their in vivo functions have been hampered by the molecular and functional diversity of GPCRs and the paucity of ligands with specific signaling effects. To better compare the effects of activating different G-protein signaling pathways through ligand-induced or constitutive signaling, we developed a new series of RASSLs (receptors activated solely by synthetic ligands) that activate different G-protein signaling pathways. These RASSLs are based on the human 5-HT(4b) receptor, a GPCR with high constitutive G(s) signaling and strong ligand-induced G-protein activation of the G(s) and G(s/q) pathways. The first receptor in this series, 5-HT(4)-D(100)A or Rs1 (RASSL serotonin 1), is not activated by its endogenous agonist, serotonin, but is selectively activated by the small synthetic molecules GR113808, GR125487, and RO110-0235. All agonists potently induced G(s) signaling, but only a few (e.g., zacopride) also induced signaling via the G(q) pathway. Zacopride-induced G(q) signaling was enhanced by replacing the C-terminus of Rs1 with the C-terminus of the human 5-HT(2C) receptor. Additional point mutations (D(66)A and D(66)N) blocked constitutive G(s) signaling and lowered ligand-induced G(q) signaling. Replacing the third intracellular loop of Rs1 with that of human 5-HT(1A) conferred ligand-mediated G(i) signaling. This G(i)-coupled RASSL, Rs1.3, exhibited no measurable signaling to the G(s) or G(q) pathway. These findings show that the signaling repertoire of Rs1 can be expanded and controlled by receptor engineering and drug selection.